Viral Hepatitis

A Study of Hyperbilirubinemia with Acholuria in Convalescence

ALLAN G. REDEKER, *M.D.*, Los Angeles, and ARTHUR KAHN, Kansas City, Kansas

• **In 42 patients convalescing from viral hepatitis, the total and 1-minute serum bilirubin levels were measured on the day bilirubin was first demonstrated to be absent from the urine.**

The levels of total bilirubin ranged from 0.5 to 6.2 per 100 ml. of blood (mean 2.8 mg.), while the levels of the 1-minute bilirubin ranged from 0.3 to 3.3 mg. per 100 ml. of blood (mean 1.5 mg.).

The reason for acholuria in the presence of the elevated 1-minute direct van den Bergh measurements is not clear, but may be due to the failure of the van den Bergh reaction to accurately measure the exact concentrations of free and conjugated bilirubin present in the plasma.

EARLY IN THE COURSE of viral hepatitis, bilirubin may appear in the urine before an increase in the total or 1-minute bilirubin level in the blood.[3] On the other hand, Watson[6] pointed out that during the late defervescent stage of infectious hepatitis, bilirubinuria may be absent in the presence of surprisingly high levels of total and 1-minute serum bilirubin.

The study here reported was made in order to further document the relationship of serum and urine bilirubin levels during the defervescent stage of viral hepatitis and to attempt to correlate the 1-minute and indirect bilirubin levels in the blood with the disappearance of bilirubin from the urine.

METHODS

Forty-two patients with acute viral hepatitis were the subjects of this study. Four were presumed (from clinical history) to have serum hepatitis, and the remainder infectious hepatitis. All patients were in hospital during the course of the study. The diagnosis of acute viral hepatitis was based on history, clinical and biochemical features. As soon as the diagnosis of acute hepatitis was ascertained, the first morning urine specimen was examined daily for bilirubin. The Ictotest,®* which is sensitive to 0.05 mg. of bilirubin per 100 ml. of urine,[2] was used for the daily qualitative urine bilirubin determinations. On the first day that a negative result by the Ictotest examination was obtained, a specimen of blood was then taken for determination of the 1-minute direct and total bilirubin by the van den Bergh reaction. On the succeeding day, the urine was again examined for bilirubin. In no instances did bilirubinuria reappear at that time, although in a few instances mild relapses with bilirubinuria did occur some days later.

RESULTS

The results of the serum van den Bergh reaction on the day the urine was first free of bilirubin (as determined by the Ictotest) are recorded in Table 1.

Twenty-seven of the 42 patients (64.3 per cent) had 1-minute direct-acting serum bilirubin levels which equaled or exceeded the indirect value at a time when the urine was free of bilirubin. Moreover, 11 of the 42 patients (26 per cent) had a 1-minute serum bilirubin greater than 2.0 mg. per 100 ml. Thirty-eight patients (90.5 per cent) had a total serum bilirubin greater than 1 mg. per 100 ml., and in the remaining four cases the 1-minute direct fraction was abnormally elevated, averaging 68 per cent of the total.

DISCUSSION

Neefe and Reinhold demonstrated bilirubin in the urine in 75 per cent of a group of patients with early, developing infectious hepatitis when the 1-minute direct bilirubin was less than 0.25 mg. per ml. of blood.[3] In marked contrast, in the current study of patients convalescing from viral hepatitis, the urine was free of bilirubin although the 1-minute direct measurement invariably exceeded 0.3 mg. per 100 ml. of blood and ranged as high as 3.3 mg. per 100 ml. In fact, the mean level of 1-minute direct bilirubin associated with acholuria was 1.5 mg. per 100 ml. of blood. It should be noted, however, that there was considerable variability in the blood levels of total and 1-minute direct bilirubin at which acholuria first appeared. It is apparent that there is no predictable level of either fraction at which acholuria can be expected in convalescent viral hepatitis.

From the Department of Medicine, School of Medicine, University of Southern California, Los Angeles; and the John Wesley County Hospital, Los Angeles.

Submitted May 21, 1962.

*A simplified test for determination of bilirubin in the urine. Material supplied by Ames Laboratories.

TABLE 1.—*Results of Bilirubin Determinations in 42 Patients Convalescing from Viral Hepatitis*

Case No.	Total Serum mg. per 100 ml.	Indirect mg. per 100 ml.	1-minute van den Bergh mg. per 100 ml.	Per Cent Direct
1.	2.8	0.9	1.9	67.8
2.	5.3	2.8	2.5	47.2
3.	6.2	3.4	2.8	45.2
4.	3.5	1.5	2.0	57.2
5.	1.3	1.0	0.3	23.1
6.	3.8	1.6	2.2	57.9
7.	4.2	1.7	2.5	59.5
8.	1.8	0.9	0.9	50.0
9.	2.5	1.2	1.3	52.0
10.	3.1	1.5	1.6	51.6
11.	3.3	1.9	1.4	42.4
12.	0.7	0.3	0.4	63.0
13.	3.7	1.9	1.8	48.7
14.	4.4	2.3	2.1	47.7
15.	2.3	0.6	1.7	73.9
16.	4.4	2.5	1.9	43.2
17.	2.0	1.0	1.0	50.0
18.	2.5	1.0	1.5	60.0
19.	5.8	2.5	3.3	56.9
20.	4.1	1.8	2.3	56.2
21.	1.4	0.5	0.9	64.3
22.	0.7	0.3	0.4	57.2
23.	2.4	1.2	1.2	50.0
24.	5.0	2.2	2.8	56.0
25.	3.2	1.8	1.4	43.8
26.	1.3	0.8	0.5	38.5
27.	2.0	1.1	0.9	45.0
28.	1.5	0.9	0.6	40.0
29.	3.7	1.6	2.1	56.8
30.	1.9	0.9	1.0	52.6
31.	2.2	1.3	0.9	40.9
32.	2.9	1.4	1.5	51.7
33.	2.7	1.4	1.3	48.3
34.	2.1	0.5	1.6	76.2
35.	2.1	0.5	1.6	76.2
36.	2.9	1.5	1.4	48.3
37.	3.1	1.3	1.8	58.1
38.	1.6	0.8	0.8	50.0
39.	0.8	0.4	0.4	50.0
40.	0.5	0.0	0.5	100.0
41.	2.8	1.4	1.4	50.0
42.	5.0	2.7	2.3	46.0
Mean	2.8	1.3	1.5	54.0
Standard deviation	±1.41	±0.73	±0.74	±12.6

Current concepts of bilirubin metabolism imply that only bilirubin in a conjugated form escapes into the urine.[4] Bilirubinuria, then, should be expected whenever the level of conjugated bilirubin in the plasma exceeds the "renal threshold." The results of this study are difficult to explain in the light of these concepts.

The possibility that the "renal threshold" for conjugated bilirubin is altered during the course of viral hepatitis seems unlikely. On the other hand, neither our data nor those of Watson[6] suggest that the injured liver in the convalescent phase of hepatitis has become diminished in its efficiency for bilirubin conjugation. On the contrary, in the present study the direct 1-minute fraction averaged 54 per cent of the total serum bilirubin in the convalescing hepatitis patients.

Possibly conjugates of bilirubin other than glucuronides—conjugates that are less readily excreted into the urine—are formed during the course of viral hepatitis. On the other hand, due to the complex kinetics of the van den Bergh reaction, the direct 1-minute fraction cannot be taken as an exact measure of the concentration of conjugated bilirubin. Brodersen,[1] in a study of the velocities of the phases of the diazo reaction, showed that serum with a reaction velocity like that obtained with free bilirubin may give as much as 30 per cent direct bilirubin in the routine van den Bergh procedure. In the routine van den Bergh procedure, the total bilirubin is estimated after the addition of an accelerator, alcohol, which allows the free bilirubin to come into solution and react with the diazotized sulfanilic acid. The possible presence of other hydrophilic substances in plasma with solubilizing properties similar to those of alcohol has been mentioned.[5] It is possible that such substances collect in the plasma during the course of viral hepatitis, distorting the results of the van den Bergh reaction in the convalescent phase of the disease.

2025 Zonal Avenue, Los Angeles 33 (Redeker).

REFERENCES

1. Brodersen, R.: Kinetics of the van den Bergh reaction. Scand. J. Clin. & Lab. Invest., 12:25, 1960.

2. Free, A. H. and Free, H. M.: A simple test for urine bilirubin. Gastroenterology, 24:414, 1953.

3. Neefe, J. R. and Reinhold, J. G.: Laboratory aids in the diagnosis and management of infectious (epidemic) hepatitis. Gastroenterology, 7:393, 1946.

4. Schmid, R.: Some aspects of bile pigment metabolism. Clin. Chem. (Supp.), 3:394, 1957.

5. Schmid, R.: Jaundice and bilirubin metabolism. Arch. Int. Med., 101:669, 1958.

6. Watson, C. J.: Some newer concepts of the natural derivatives of hemoglobin. Blood, 1:99, 1946.